REMARKS

Applicants gratefully acknowledge courtesies extended during an interview with Dr. Li at the USPTO on March 3, 2005 ("Interview"). The Examiner made several helpful comments which have been used as a basis for this submission.

Support for the present claim amendments can be found throughout the instant application including the drawings and claims as filed originally.

For instance, particular support for new claims 68-69 can be found on Pg. 10, first full paragraph. Claims 68 and 69 are being added in line with a suggestion by the Examiner during the interview.

New claims 70-72 find specific support at pgs. 14, lines 19-27; pg. 30, lines 4-13; and Example 14, for instance.

No new matter has been added by virtue of the present claim amendments or new claims.

35 USC §112, first paragraph (written description)

Claims 29-67 stand rejected under §112, first paragraph (written description) on grounds that the specification does not describe the invention claimed. While Applicants respectfully disagree with each position taken, bases for the rejections have been addressed.

In particular, the phrase "the functional fragment of the TM has at least about 85% of the protein C binding activity of human thrombomodulin" has been removed from independent claims 29, 30, 52, 56, and 59. Related language as set forth in steps (b)-(c) (now struck out by amendment) have been removed at the suggestion of the Examiner during the Interview.

Turning to pg. 3 of the Action, claims 29, 52, 56 and 59 have been amended to point out "vascular graft" with more particularity.

At pg. 5 of the Action, the Office noted that the specification was enabling "for treatment of a mammal to resist early vascular graft failure using *autologous* vascular graft,.." . Claims 29, 30, 52, 56, and 59 have been amended accordingly.

In view thereof, reconsideration and withdrawal of the rejections are respectfully requested.

35 USC §112, second paragraph

Claims 29, and 31-67 stand rejected under 35 USC § 112, second paragraph, as being indefinite. While Applicants disagree, basis for the rejection has been addressed. In particular, a step suggested by the Examiner during the Interview has been added to the independent claims ie., "b) transplanting the graft into the mammal". Certain other steps have been canceled at the suggestion of the Examiner.

The rejection as to claim 34 has been addressed.

In view thereof, reconsideration and withdrawal of the rejections are requested.

35 USC §103

Claim 51 stands rejected as being unpatentable over Waugh et al. (Cir. Res. 1999 84: 84-92; hereinafter "Waugh"). The claim was further rejected over Esmon et al. (USP 5,804,392) or Fukudome et al. (USP 5,852,171). While Applicants respectfully disagree with the stated reasons for the rejection, it is moot in view of the present submission. Claim 51 has been canceled.

A. Claims 29-50, 52, 59, 60 and 61 stand rejected as being unpatentable over Vasselli et al. (Cardiovasc. Res. 1997: 35: 459) in view of Waugh and Thomas et al. (Transplant 1999: 68:1660).

Before turning to basis for the rejection, Applicants believe a brief overview would be helpful.

There is recognition in the field that nearly all blood vessels have three layers: the intima, media and the adventitia. Arteries are thought to have a well-developed media layer of smooth muscle cells that help arteries withstand high blood pressure. The arterial intima is a single layer of *endothelial cells* that line the lumen. Endothelial cells express thrombomodulin (TM) in relatively large amounts. An important function of the expressed TM is to prevent blood clotting.

There is understanding in the field that arterial angioplasty (especially as taught by Waugh) involves inflating a balloon within the artery. That stretches and damages the artery and *destroys the intimal endothelial cells.* Loss of endothelial cells (and the TM formerly produced by the cells) leaves the artery susceptible to acute thrombosis (which can occur within minutes or days). The balloon damage also causes the medial smooth muscle cells to proliferate and form what is called a *neointima*. Neointimal formation often causes restenosis after coronary angioplasty (a process that takes 2-8 months).

Waugh as relied on by the USPTO taught that TM overexpression can prevent clots from forming at the site of balloon injury of an *artery*. Endothelial cells that make TM were *stripped away* by the balloon. Waugh taught overexpressing TM in smooth muscles cells of the injured *artery* using adenoviral mediate gene transfer.

In marked contrast, the presently claimed invention is completely different from Waugh as relied on, either taken alone or in combination with Vassalli and Thomas.

For instance, the claimed invention relates to methods that feature introducing particular nucleic acids into an autologous *vein graft*. In marked contrast, Waugh teaches overexpression of TM to prevent thrombus formation in an artery graft.

The differences between vein and artery grafts (as provided by Waugh) are substantial and non-obvious. For instance, a worker reading Applicants' disclosure would understand that vein grafts, especially when used according to Applicants' invention, are generally susceptible to thrombosis and neointimal hyperplasia. The endothelium of the vein graft remains intact. In marked contrast, Waugh's arteries have no endothelium because it was stripped away by balloon damage. What Waugh showed, as relied on, was that a worker could overexpress TM to prevent acute clots and that the TM could prevent the growth of medial smooth muscle cells, thereby reducing neointima formation. There is certainly no specific teaching or suggestion in the cited Waugh reference (taken alone or in combination with Vasselli and Thomas) that one could resist early graft failure by employing an autologous vein graft as Applicants have done.

Additionally, the claimed method feature the introduction of certain nucleic acid into *endothelial cells* of the vein graft. In marked contrast, Waugh, as cited, teaches introduction of TM into the arterial smooth muscle cells. Waugh did not teach or suggest introducing agent into endothelial cells because those cells were stripped away by the balloon injury.

There is certainly no specific teaching or suggestion in the cited references that one could introduce nucleic acid into the *endothelial cells* of the vein graft, according to the instant specification.

None of Vassalli and Thomas, as relied on, remedies these deficiencies. Moreover, the Office's combination of Waugh, Vassalli and Thomas, does not teach, suggest or provide any motivation to make or use the presently claimed invention.

For these reasons alone, Applicants respectfully request reconsideration and withdrawal of the obviousness rejection.

B. Claims 53-55 and 62-64 stand rejected as obvious over Vassalli, in view of Waugh, and Thomas, taken further with Hardy et al. (*J. Virol.* 1997 71: 1842; "Hardy"). Applicants respectfully traverse the rejection.

The deficiencies of Waugh, Vassalli and Thomas, as cited by the Office, have been discussed above in view of the pending claims. Hardy as cited does not remedy these defects.

Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

C. Claims 56-58, and 65-67 stand rejected as obvious over Vassalli, in view of Waugh, and Thomas, taken further with Qing et al. (J. Virol. 1997 71: 5663-7; "Qing"). Applicants respectfully traverse the rejection.

The shortcomings of Waugh, Vassalli and Thomas, as cited by the Office, have been discussed above in view of the pending claims. Qing as cited does not remedy these defects.

Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

It is believed that the application is in condition for allowance, which action is earnestly solicited. Although it is not believed that any fee is needed to consider this

submission, the USPTO is authorized to charge our deposit account no. **04-1105** should such fee be deemed necessary.

Respectfully submitted,

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By: _____

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